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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of	)	Mail Stop AMENDMENT
BERNDL et al.	)	Confirmation No.: 4232
Serial No. 09/914,795	)	Examiner: GOLLAMUDI
Filing or 371(c) Date: September 5, 2001	)	Art Unit: 1616

For: A PROCESS FOR PRODUCING SOLID CYCLODEXTRIN-CONTAINING DOSAGE FORMS

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SUBMISSION OF VERIFIED TRANSLATION OF PRIORITY DOCUMENT

In supplement to the reply of June 30, 2005, applicants enclose herewith a verified translation of the priority document.

Please charge any shortage in fees due in connection with the filing of this paper to Deposit Account No. 14.1437. Please credit any excess fees to such account.

Respectfully submitted,
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UNITED STATES PATENT AND TRADEMARK OFFICE

I, Susan ANTHONY BA, ACIS,

Director of RWS Group Ltd, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the German and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 12 March 1999 under the number 199 11 097.2 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group Ltd

The 22nd day of June 2005

FEDERAL REPUBLIC OF GERMANY

Certificate

BASF Aktiengesellschaft
of
Ludwigshafen/Germany

have filed a Patent Application under the title:

"A process for producing solid cyclodextrin-containing dosage forms"

on 12 March 1999 at the German Patent and Trademark Office.

The attached documents are a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent and Trademark Office has for the time being given the Application the symbols C 08 B, B 01 J and A 61 K of the International Patent Classification.

Munich, 17 March 2000
German Patent and Trademark Office
The President
pp
Dzierzon

File No: 199 11 097.2

A process for producing solid cyclodextrin-containing dosage forms

The present invention relates to a process for producing solid dosage forms comprising as components at least one physiologically tolerated polymeric binder, at least one active ingredient and at least one cyclodextrin.

The group of cyclodextrins comprises important excipients for manufacturing foodstuffs, cosmetics, pharmaceuticals and pesticides, and is also of importance in a number of analytical and industrial separation problems. Most of the interesting properties of cyclodextrins derive from their ability to form so-called guest-host systems with host molecules.

Cyclodextrins have been used for some time in pharmaceutical compositions in order to modify the properties of the dosage forms or of the active ingredients employed therein. The observed modified properties of active ingredients in the presence of cyclodextrins are generally attributed to the formation of cyclodextrin-active ingredient complexes. Such cyclodextrin-active ingredient complexes often show improved chemical properties such as, for example, increased stability to the effects of light and temperature, oxidation, reduction, hydrolysis and dehydration, and/or altered physical properties such as, for example, changes of state or changes in the rheological properties. Cyclodextrins are also known to have an effect on the taste or odor of active ingredients.

Cyclodextrins can be processed in dosage forms in several ways. On the one hand, the cyclodextrin can be admixed in crystalline form, for example as powder or granules, with the binder and active ingredient and then, where appropriate after homogenization, compressed to give the dosage form, for example by conventional tableting processes.

However, additional process steps are usually necessary for producing cyclodextrin-active ingredient complexes. One such process is complexation of active ingredients with cyclodextrins in aqueous suspension or solution. A disadvantage of this process is that the resulting cyclodextrin-active ingredient complex must be worked up, that is to say usually separated off and/or dried. An increased rate of complexation of active ingredients in aqueous suspension or solution is reported by T. Loftsson et al., Proc. Int. Symp. Cyclodextrines 8 (1996) 399-402 and Pharmazie 1998 (53) 11, 733-740, when water-soluble polymers are added in

the complexation. It is postulated that a ternary intermediate is formed.

For example, WO 98/55148 discloses a cyclodextrin-containing pharmaceutical composition in which an active ingredient, citric acid, hydroxypropylcellulose and a cyclodextrin are dissolved in alcohol, and the alcohol is then evaporated off. The resulting gel is packed into gelatin capsules.

In order to keep the amount of solvents employed low, WO 94/11031 and FR-A 2705677 recommend producing cyclodextrin-active ingredient complexes by extruding melts of cyclodextrin and active ingredient which are moist with solvent. Solvents mentioned as suitable are, inter alia, water, methanol or ethanol, in amounts of from 20 to 90% of the weight of the melt for extrusion.

WO 97/18839 describes a process for producing solid mixtures of cyclodextrins and active ingredients by melt extrusion, where the active ingredient is embedded in the cyclodextrin carrier. After the resulting extrudate has solidified it is ground and employed, with the addition of binders, for producing dosage forms. Barrel temperatures of at least 239°C are necessary for this process.

The production of dosage forms by melt extrusion has been known for some time. This entails continuous extrusion of an active ingredient-containing, usually solvent-free melt of a polymeric active ingredient-containing binder, and shaping the extrudate to the required dosage form, for example in a calender with molding rolls or molding belts, see EP-A-240 904, EP-A-240 906 and EP-A-358 105.

However, there is still a need for dosage forms with active ingredient release tailored to requirements, in particular with faster release of active ingredient.

It is an object of the present invention to provide a simple process for producing solid dosage forms with faster release of active ingredient.

We have found that this object is achieved when a plastic mixture of binder and active ingredient is formed in the presence of cyclodextrins, and this mixture is shaped to the dosage form. It was surprising in particular that this process affords dosage forms with faster release of active ingredient without the need

to produce a cyclodextrin-active ingredient complex in elaborate preceding process steps.

The present invention therefore relates to a process for producing solid dosage forms comprising as components at least one physiologically tolerated polymeric binder, at least one active ingredient and at least one cyclodextrin, wherein the components are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to the dosage form.

The term "dosage form" refers herein to any form for administering active ingredients to humans, animals or plants. The dosage forms obtained according to the invention are particularly suitable for oral or rectal administration or as implantable active ingredient depots for humans and animals. Particularly preferred dosage forms are tablets of every shape, coated tablets, pellets and suppositories.

Polymeric binders suitable for the process according to the invention are those which are physiologically tolerated appropriate for the particular purpose of use of the dosage form. The polymeric binders preferably form a polymer matrix after solidification, and are at least partly soluble or swellable in a physiological medium. Examples of suitable polymeric binders are:

synthetic polymers such as polyvinyllactams, in particular polyvinylpyrrolidone (PVP), copolymers of vinyllactams such as N-vinylpyrrolidone, N-vinylpiperidone and N-vinyl-ε-caprolactam, but especially N-vinylpyrrolidone, with (meth)acrylic acid, (meth)acrylates, vinyl esters, in particular vinyl acetate, copolymers of vinyl acetate and crotonic acid, partly hydrolyzed polyvinyl acetate, polyvinyl alcohol, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylates, polymethacrylates and copolymers of dimethylaminoethyl acrylates and methacrylates (for example Eudragit types), polyalkylene glycols such as polypropylene glycols and polyethylene glycols, preferably with molecular weights above 1000, particularly preferably above 2000 and very particularly preferably above 4000 (for example polyethylene glycol 600, polyethylene glycol 6000), copolymers of methyl methacrylate and acrylic acid, polyacrylamides, polyvinylformamide (where appropriate partially or completely hydrolyzed),

modified natural polymers, for example modified starches and modified celluloses, such as cellulose esters, cellulose ethers, especially methylcellulose and ethylcellulose,

hydroxyalkylcelluloses, in particular hydroxypropylcellulose, hydroxyalkylalkylcelluloses, in particular hydroxypropylmethylcellulose or hydroxypropylethylcellulose, cellulose phthalates, in particular cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate, and

natural or predominantly natural polymers such as gelatin, polhydroxyalkanoates, for example polyhydroxybutyric acid and polylactic acid, polyamino acids, for example polylysine, polyasparagine, polydioxanes and polypeptides and mannans, especially galactomannans.

Of these, the synthetic and modified natural polymers are preferred, and the synthetic polymers are particularly preferred.

Preferred polymeric binders among these are polyethylene glycol, alkylcelluloses and hydroxyalkylcelluloses, in particular hydroxypropylcellulose and hydroxypropylmethylcellulose, poly(hydroxyalkyl acrylates) and poly(hydroxyalkyl methacrylates), polyacrylates and polymethacrylates, polyvinylpyrrolidone, copolymers containing N-vinyllactams, especially N-vinylpyrrolidone, and vinyl esters, especially vinyl acetate, copolymers containing N-vinyllactams, in particular N-vinylpyrrolidone, and (meth)acrylates, and mixtures thereof.

Particularly preferred polymeric binders are polyethylene glycol, in particular with molecular weights above 1000 and preferably above 4000, polyvinylpyrrolidone, copolymers containing N-vinylpyrrolidone and vinyl acetate, and mixtures thereof.

Binders advantageously used as polymeric binders are those which have a K value (according to H. Fikentscher, Cellulose-Chemie 13 (1932), pp. 58-64 and 71-74) in the range between 10 and 100, in particular between 15 and 80.

In particular embodiments of the process according to the invention, the cyclodextrin can be present partly or completely chemically bound to the polymeric binder.

The plastic mixture usually has a content of polymeric binder in the range from 5 to 99.8% by weight, preferably from 10 to 98% by weight and particularly preferably from 15 to 80% by weight.

Active ingredients for the purpose of the invention are all substances with a pharmaceutical effect and minimal side effects as long as they decompose negligibly under the processing conditions. The amount of active ingredient per dose unit and the

concentration may vary within wide limits depending on the activity and release rate. The only condition is that they suffice to achieve the desired effect. Thus, the active ingredient concentration may be in the range from 0.01 to 60% by weight, preferably 0.5 to 30% by weight, and in particular 1 to 25% by weight. It is also possible to employ combinations of active ingredients. Active ingredients for the purpose of the invention are also vitamins, minerals and plant extracts or plant preparations with pharmaceutically active constituents, and plant treatment agents and insecticides. The vitamins include the vitamins of the A group, the B group, by which are meant besides B_1, B_2, B_6 and B_{12} and nicotinic acid and nicotinamide also compounds with vitamin B properties such as adenine, choline, pantothenic acid, biotin, adenylic acid, folic acid, orotic acid, pangamic acid, carnitine, p-aminobenzoic acid, myo-inositol and lipoic acid and vitamin C, vitamins of the D group, E group, F group, H group, I and J groups, K group and P group. The plant extracts or plant preparations include, for example, dry plant extracts, in particular St. John's wort extract, milk thistle extract, cava-cava extract, celandine extract, Gingko biloba extract, and essential oils, especially garlic oil, camomile oil, peppermint oil, caraway oil and eucalyptus oil. Active ingredients for the purpose of the invention also include therapeutic peptides and vaccines.

The process according to the invention is suitable, for example, for processing the following active ingredients or the pharmacologically active salts thereof:

acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir, alfacalcidol, allantoin, allopurinol, alprazolam, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclomethasone, benexate, benserazide, benzalkonium hydrochloride, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperiden, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefachlor, cefadroxil, cefalexin, cefazoline, cefixime, cefotaxime, cefotiam, ceftazidime, ceftriaxone, cefuroxime, chloramphenicol, chlordiazepoxide, chlorhexidine, chlorpheniramine, chlortalidone, choline, cyclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, codeine, cholestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan,

dextropropoxiphene, diazepam, diclofenac, digoxin, digitoxin, dihydrocodeine, dihydroergotamine, dihydroergotoxin, diltiazem, diphenhydramine, dipyridamole, dipyrone, disopyramide, domperidone, dopamine, doxycycline, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus globulus, famotidine, felodipine, fenofibrate, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, folinic acid, furosemide, gallopamil, gemfibrozil, gentamicin, Gingko biloba, glibenclamide, glipizide, clozapine, Glycyrrhiza glabra, griseofulvin, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, imipramine, indomethacin, iohexol, iopamidol, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, itraconazole, iodine, ketotifen, ketoconazole, ketoprofen, ketorolac, garlic oil, labetalol, lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, methyldopa, methylprednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamin mixtures or combinations and mineral salts, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nicardipine, nicergoline, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrazepam, nitrendipine, nitroglycerine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptyline, nystatin, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, pentoxifylline, phenobarbital, phenoxymethylpenicillin, phenylephrine, phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazepam, prazosin, prednisolone, prednisone, propafenone, propanolol, prostaglandins, proxyphylline, pseudophedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, selegiline, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulfasalazine, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, tetracycline, theophylline, thiamine, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, troxerutin, thiaprofenic acid, uracil, valproic acid, vancomycin, verapamil, vitamin E, zidovudine.

Preferred active ingredients are ibuprofen (as racemate, enantiomer or enriched enantiomer), ketoprofen, flurbiprofen, benexate, cefotiam, chlordiazepoxide, digitoxin, thiaprofenic acid, garlic oil, diazepam, piroxicam, itraconazole, ketoconazole, iodine, nystatin, prostaglandins, hydrocortisone, dexamethasone, estradiol, verapamil, nifedipine, nitrogycerine, omeprazole, ranitidine, cyclosporin, trandolapril and therapeutic peptides.

Cyclodextrins for the purpose of the invention are cyclic oligo- or polysaccharides, for example so-called cycloamyloses or cycloglucans, and analogous cyclic carbohydrates which are described, for example, in Angew. Chem. 92 (1980) p. 343 or F. Vögtle, Supramolekulare Chemie, 2nd Edition, (1992). Suitable and preferred are those cyclodextrins which have a structure suitable for interactions with active ingredient molecules, in particular in the sense of host-guest systems. Particularly suitable cyclodextrins are those consisting of 6, 7, 8 or 9 α-1,4-glycosidically linked glucose units, which are called α-, β-, γ- or δ-cyclodextrins. Higher structures analogous to cyclodextrins and composed of a larger number of glucoses or similar sugars are also conceivable and suitable.

Also suitable as cyclodextrins are modified cyclodextrins such as, for example, products which can be prepared by reacting cyclodextrins with alkylene oxides, alkyl halides, acid chlorides, epichlorohydrins, isocyanates or halogenated carboxylic acids. Thus, suitable examples are products of the reaction of cyclodextrins with alkylene oxides such as ethylene oxide, propylene oxide, butylene oxide or styrene oxide. One, more than one or all hydroxyl groups in the cyclodextrin polyethers formed in this way may be substituted. Depending on the degree of substitution or the chain lengths of the polyether units, the average molar degree of substitution, that is to say the number of moles of alkylene oxide with which one mole of cyclodextrin is reacted, is usually between 3 and 20,000, but there is in principle no upper limit. Particularly suitable examples are the products of the reaction of cyclodextrins with alkylating agents such as C_1-C_{22}-alkyl halides, for example methyl chloride, ethyl chloride, isopropyl chloride, n-butyl chloride, isobutyl chloride, benzyl chloride, lauryl chloride, stearyl chloride, methyl bromide, ethyl bromide, n-butyl bromide and dialkyl sulfates such as, for example, dimethyl sulfate or diethyl sulfate. Reaction with alkylating reagents leads to cyclodextrin ethers in which one, more than one or all hydroxyl groups are substituted by alkyl ether groups. With the cyclodextrins composed of glucose units, the average degree of

etherification per glucose unit is usually in the range from 0.5 to 3, preferably in the range from 0.1 to 2.5 and particularly preferably in the range from 1 to 2. Particular preference is given to methylated, ethylated or propylated α-, β- or γ-cyclodextrins with an average degree of etherification of from 1.5 to 2.2. Also suitable are cyclodextrin esters which are obtainable by reacting cyclodextrins with acid chlorides such as carbonyl or sulfonyl chlorides. Particularly suitable are carbonyl chlorides such as acetyl chloride, acryloyl chloride, (meth)acryloyl chloride or benzoyl chloride.

Also suitable are polymer-modified cyclodextrins, that is to say cyclodextrins which are incorporated into the main chain of polymers and/or cyclodextrins which have been attached to side chains of polymers or are themselves side chains of polymers. Polymer-modified cyclodextrins in which the cyclodextrin units are arranged in the main chain of the polymer can be obtained, for example, by reacting cyclodextrins with or in the presence of suitable coupling or crosslinking reagents, for example as described in Helv. Chim. Acta, Vol. 48, (1965), p. 1225. Polymer-modified cyclodextrins in which the cyclodextrin units are side chain constituents or act as side chains can be obtained, for example, by cyclodextrins modified with polymerizable groups being polymerized with other comonomers, for example by polymerizing cyclodextrin (meth)acrylates in the presence of other ethylenically unsaturated monomers or by free-radical grafting of cyclodextrin (meth)acrylates onto polymers with free hydroxyl groups such as, for example, polyvinyl alcohol. Another possibility for preparing polymer-modified cyclodextrins with the cyclodextrin units on side groups or as side groups of polymers is to react cyclodextrins, deprotonated cyclodextrins or their alkali metal salts with polymers which have complementary reactive groups such as, for example, anhydride, isocyanate, acid halide or epoxy groups or halogens.

Further suitable polymer-modified cyclodextrins and processes for their preparation are described in DE-A 196 42 768, which is incorporated herein by reference.

It is also possible to employ those polymer-modified cyclodextrins in which the polymer content of the polymer modification itself represents the polymeric binder.

This is the case in particular when the molecular weight of such polymer-modified cyclodextrins is above 10,000, preferably above 20,000 or 50,000. In these cases, the cyclodextrin is in a form chemically bound to the polymeric binder.

In the case of polymer-modified cyclodextrins and cyclodextrins which are chemically bound to the polymeric binder, which have molecular weights above 30,000, the polymer content must be included in the total polymer content of the plastic mixture. In the case of polymer-modified cyclodextrins and cyclodextrins which are chemically bound to the polymeric binder, which have molecular weights above 30,000, the cyclodextin content must be included in the total cyclodextrin content of the plastic mixture. Examples of suitable cyclodextrins chemically bound to the polymeric binder are appropriately high molecular weight polyalkylene ether-modified cyclodextrins or cyclodextrin (meth)acrylate copolymers with (meth)acrylic acid, (meth)acrylates, vinyl acetate and/or N-vinylpyrrolidone as comonomers.

The plastic mixture may comprise from 0.1 to 90% by weight, preferably from 0.5 to 70% by weight and particularly preferably from 1 to 60% by weight of at least one cyclodextrin. The amount of cyclodextrin is preferably chosen so that the molar ratio between active ingredient and cyclodextrin is in the range from 0.1 to 4.0, preferably in the range from 0.5 to 3 and particulalry preferably in the range from 0.8 to 2.0. In preferred embodiments of the process according to the invention, it has proven advantageous to employ active ingredient and cyclodextrin in approximately equimolar amounts.

It is also possible to employ in the process according to the invention excipients, for example those which facilitate production of the dosage forms and/or improve the properties of the resulting dosage forms.

Examples of such excipients are conventional pharmaceutical excipients, the total amount of which can be up to 100% of the weight of the polymeric binder, for example extenders and bulking agents such as silicates or diatomaceous earth, magnesium oxide, aluminum oxide, titanium oxide, methylcellulose, sodium carboxymethylcellulose, sugar alcohols such as, for example, mannitol, sorbitol, xylitol and isomalt, talc, sucrose, lactose, cereal or corn starch, potato flour, polyvinyl alcohol, in particular in a concentration of from 0.02 to 50, preferably 0.20 to 20, % of the total weight of the mixture;

lubricants and release agents such as magnesium, aluminum and calcium stearates, talc and silicones, and animal and vegetable fats, especially in hydrogenated form and which are solid at room temperature. These fats preferably have a melting point of 30°C or above. Triglycerides of C_{12}, C_{14}, C_{16} and C_{18} fatty acids are preferred. Waxes, such as carnauba wax, can also be used. These fats and waxes may advantageously be admixed alone or together with mono- and/or diglycerides or phosphatides, in particular lecithin. The mono- and diglycerides are preferably derived from the abovementioned fatty acid types. The total amount of lubricants and release agents is preferably from 0.1 to 10% of the total weight of the composition for a particular layer;

flow regulators, for example Aerosil, in an amount of from 0.1 to 5% of the total weight of the mixture;

dyes such as azo dyes, organic or inorganic pigments or dyes of natural origin, preference being given to inorganic pigments in a concentration of from 0.001 to 10, preferably 0.5 to 3, % of the total weight of the mixture;

stabilizers such as antioxidants, light stabilizers, hydroperoxide destroyers, radical scavengers, stabilizers against microbial attack.

It is also possible to add wetting agents, preservatives, disintegrants, adsorbents and mold release agents, and surfactants, preferably anionic and nonionic surfactants, such as, for example, soaps and soap-like surfactants, alkyl sulfates and alkylsulfonates, salts of bile acids, alkoxylated fatty alcohols, alkoxylated alkylphenols, alkoxylated fatty acids and fatty acid glycerol esters, which may be alkoxylated, and solubilizers such as Cremophor (polyethoxylated castor oil), Gelosire, vitamin E TPGS and Twenn (ethoxylated sorbitan fatty acid esters) (cf. for example, H. Sucker et al. Pharmazeutische Technologie, Thieme-Verlag, Stuttgart 1978).

Excipients for the purpose of the invention also means substances for producing a solid solution with the active pharmaceutical ingredient. Examples of these excipients are pentaerythritol and pentaerythritol tetraacetate, urea, phosphatides such as lecithin, polymers such as, for example, polyethylene oxides and polypropylene oxides and their block copolymers (poloxamers), homo- and copolymers of vinylpyrrolidone, especially copolymers of vinylpyrrolidone and vinyl acetate, poly(meth)acrylates (for example Eudragit types), surfactants such as polyoxyethylene 40 stearate, and citric and succinic acids, bile acids, sterols and

others as indicated, for example, by J. L. Ford, Pharm. Acta Helv. 61, (1986), pp. 69-88.

Pharmaceutical excipients also include additions of bases and acids to control the solubility of an active ingredient (see, for example, K. Thoma et al., Pharm. Ind. 51, (1989), pp. 98-101).

The only preconditions for suitability of excipients are adequate thermal stability and compatibility with the active ingredient used.

To form the plastic mixture it is necessary to mix and convert into the plastic state the ingredients, namely at least one thermoplastic, physiologically tolerated binder and at least one active ingredient and at least one cyclodextrin. The plastic mixture is preferably formed without addition of a solvent. Solvents for the purpose of the invention are low molecular weight volatile liquids, for example water, C_1-C_6-monoalcohols and their ethers, esters of C_1-C_6-monoalkanols with C_1-C_6-carboxylic acids, alkanes, aromatic and substituted aromatic compounds with up to 12 carbon atoms and chlorinated hydrocarbons such as, for example, methylene chloride. Another solvent which can be used is liquid CO_2.

It may be advantageous in certain cases to add active ingredients and/or excipients as solution or suspension in a solvent, for exmaple one of the abovementioned solvents, when forming the plastic mixture. For example, active pharmaceutical ingredients are frequently used in the form of a salt, which is generally soluble in water. Water-soluble active ingredients can therefore be employed as aqueous solution or, preferably, be taken up in the aqueous solution or dispersion of the birder. A corresponding statement applies to active ingredients which are soluble in one of said solvents when the liquid form of the components used is based on an organic solvent. The components to be employed according to the invention may contain small amounts of the abovementioned solvents, for example because of hygroscopicity, solvent inclusions or water of crystallization. The total solvent content of the plastic mixture is preferably below 15%, in particular below 10% and particularly preferably below 5%.

The formation of the plastic mixture can take place by melting or else by kneading, mixing or homogenizing below the melting point of the binder. The plastic mixture is preferably formed at temperatures below 220°C. The formation of the plastic mixture preferably does not take place by forming a paste or partly

dissolving one or more components (that is to say binder, active ingredient and/or cyclodextrin) with liquids or solvents such as, for example, those mentioned above, but takes place mainly or exclusively by exposing the component(s) to thermal or themomechanical effects (that is to say by thermal plasticization). The plastic mixture is preferably formed by extrusion, particularly preferably by melt extrusion. The plasticization process steps can be carried out in a manner known per se, for example as described in EP-A-0 240 904, EP-A-0 337 256, EP-A-0 358 108, WO 97/15290 and WO 97/15291. The contents of these publications are incorporated herein by reference.

The components, that is to say binder, active ingredient and cyclodextrin and, where appropriate, excipients, can be first mixed and then converted into the plastic state and homogenized. However, it has proven to be preferred, especially on use of sensitive active ingredients, first for the polymeric binder and the cyclodextrin, where appropriate together with conventional pharmaceutical additives, to be converted into the plastic state and premixed, operating the equipment such as stirred vessels, agitators, solids mixers etc. where appropriate alternately, and then for the sensitive active ingredient(s) to be mixed in (homogenized) in plastic phase in "intensive mixers" with very short residence times. The active ingredient(s) can be employed in solid form or as solution, suspension or dispersion.

It may be advantageous in particular embodiments of the process according to the invention first to form a plastic mixture of binder and active ingredient and, where appropriate, excipients, and to add the cyclodextrin to this. This procedure may be advantageous in particular when the active ingredient has plasticizer-like properties, and the reduction in the overall process temperature which can be achieved thereby is desirable.

It may be advantageous in particular embodiments of the process according to the invention first to mix the active ingredient and cyclodextrin, and to add them to the plasticized binder. This procedure may be advantageous in particular when the active ingredient and/or the cyclodextrin is(are) thermally unstable.

The plasticizing, melting and/or mixing take place in an apparatus customary for this purpose. Particularly suitable ones are extruders or heatable containers with agitator, for example kneaders (such as of the type mentioned below).

It is also possible to use as mixing apparatus one employed for mixing in plastics technology. Suitable apparatuses are described, for example, in "Mischen beim Herstellen und Verarbeiten von Kunststoffen", H. Pahl, VDI-Verlag, 1986. Particularly suitable mixing apparatuses are extruders and dynamic and static mixers, and stirred vessels, single-shaft stirrers with stripper mechanisms, especially paste mixers, multishaft stirrers, especially PDSM mixers, solids mixers and, preferably, mixer/kneader reactors (for example ORP, CRP, AP, DTB supplied by List or Reactotherm supplied by Krauss-Maffei or Ko-Kneader supplied by Buss), trough mixers and internal mixers or rotor/stator systems (for example Dispax supplied by IKA).

In the case of sensitive active ingredients it is preferable first for the polymeric binder and the cyclodextrin to be converted into the plastic state in an extruder and then for the active ingredient to be admixed in a mixer/kneader reactor. On the other hand, with less sensitive active ingredients, a rotor/stator system can be employed for vigorously dispersing the active ingredient.

The mixing apparatus is charged continuously or batchwise, depending on its design, in a conventional way. Powdered components can be introduced in a free feed, for example via a weigh feeder. Plastic compositions can be fed in directly from an extruder or via a gear pump, which is particularly advantageous if the viscosities and pressures are high. Liquid media can be metered in by a suitable pump unit.

The mixture obtained by mixing and converting the binder and, where appropriate, the active ingredient and/or cyclodextrin and, where appropriate, the additive(s) into the plastic state is pasty, viscous or fluid (plastic) and is therefore also extrudable. The glass transition temperature of the mixture is preferably below the decomposition temperature of all the components present in the mixture.

The steps of mixing and melting in the process can be carried out in the same apparatus or in two or more separately operating apparatuses. The preparation of a premix can take place in one of the conventional mixing apparatuses described above. A premix of this type can then be fed directly, for example, into an extruder and subsequently be extruded, where appropriate with the addition of other components.

It is possible in the process according to the invention to employ as extruders single screw machines, intermeshing screw machines or else multiscrew extruders, especially twin screw extruders, corotating or counterrotating and, where appropriate, equipped with kneading disks. If it is necessary in the extrusion to evaporate a solvent, the extruders are generally equipped with an evaporating section. Particularly preferred extruders are those of the ZKS series from Werner & Pfleiderer.

The process according to the invention can also be used to produce multilayer cyclodextrin-containing dosage forms by coextrusion, in which case a plurality of mixtures of the components described above, at least one of which contains cyclodextrin(s), are fed together into an extrusion die so that the required layer structure of the multilayer dosage form results. Different binders are preferably used for different layers.

Multilayer dosage forms preferably comprise two or three layers. They can be in open or closed form, in particular as open or closed multilayer tablets.

The shaping takes place by coextrusion, with the mixtures from the individual extruders or other units being fed to a common coextrusion die. The shape of the coextrusion dies depends on the required dosage form. Suitable examples of dies are slit dies and annular dies. The design of the die moreover depends on the polymeric binder to be used and the required dosage form.

It must be possible to convert the polymeric binder into a plastic state in the complete mixture of all the components in the range from 30 to 200°C, preferably from 40 to 170°C. The glass transition temperature of the mixture must therefore be below 220°C, preferably below 180°C. If necessary, it is reduced by conventional, pharmacologically acceptable plasticizing excipients. The amount of plasticizer does not exceed 30% of the total weight of binder and plasticizer so that the drug forms are stable on storage and show no cold flow. However, the mixture preferably contains no plasticizer.

Examples of such plasticizers are:
organic, preferably involatile compounds such as, for example, C_7-C_{30}-alkanols, ethylene glycol, propylene glycol, glycerol, trimethylolpropane, triethylene glycol, butanediols, pentanols such as pentaerythritol and hexanols, polyalkylene glycols, preferably with a molecular weight of from 200 to 1000, such as, for example, polyethylene glycols, polypropylene glycols and

polyethylene/propylene glycols, silicones, aromatic carboxylic esters (for example dialkyl phthalates, trimellitic esters, benzoic esters, terephthalic esters) or aliphatic dicarboxylic esters (for example dialkyl adipates, sebacic esters, azelaic esters, citric and tartaric esters), fatty acid esters such as glycerol monoacetate, glycerol diacetate or glycerol triacetate or sodium diethyl sulfosuccinate. The concentration of plasticizer is generally from 0.5 to 15, preferably 0.5 to 5, % of the total weight of the plastic mixutre.

In preferred embodiments of the present invention, the plastic mixture is prepared by employing

a) 0.5 to 30% by weight of at least one active ingredient,
b) 0.5 to 70% by weight of at least one cyclodextrin,
c) 10 to 98% by weight of at least one polymeric binder and
d) 0 to 50% by weight of conventional excipients.

The process according to the invention can advantageously be carried out wholly or partly under sterile conditions, for example in clean rooms using sterilized equipment such as, for example, weighers, mixers, extruders and shaping machines, such as calenders, nip devices and choppers. It is possible either for the starting materials to be introduced into the process in sterilized form, where appropriate with the addition of suitable antibacterial and/or antiviral excipients, and/or for the process conditions, especially the temperature, to be chosen so that sterile dosage forms according to the invention are obtained. The resulting sterile dosage forms can then advantageously be further processed, likewise under sterile conditions, for example to parenteral products, or be packaged directly, for example by blister packing or sealing. The shaping and the packaging may also be carried out at the same time, in particular when the shaping of the plastic mixture by calendering is carried out by molding rolls. This is done by introducing, in addition to the plastic mixture, materials in the form of sheets between the melt and the molding roll in each case, whereby it is possible to achieve at the same time as the shaping of the plastic mixture to dosage forms an enveloping and/or a packaging of the dosage form, as described in WO-96/19963 which is incorporated herein by reference.

It is specifically possible for solid solutions to be formed in the process according to the invention. The term "solid solutions" is familiar to the skilled worker, for example from the literature cited at the outset. In solid solutions of cyclodextrin/active ingredient complexes or active ingredients

and/or cyclodextrins in polymers, the cyclodextrin/active ingredient complex or active ingredient and/or cyclodextrin is in the form of a molecular dispersion in the polymer.

A further advantage of the present invention is that this process can be used to produce solid dosage forms in which the active ingredient(s) and the cyclodextrin(s) interact, for example in the form of cyclodextrin/active ingredient complex formation. Preferred cyclodextrin/active ingredient complexes are so-called inclusion or host-guest complexes. Such complexes can be formed by inclusion of active ingredients in cavities of cyclodextrin aggregates, for example by what is called molecular encapsulation or by stoichiometric or approximately stoichiometric interaction of one or more active ingredient molecules with one or more cyclodextrin molecules.

The dosage forms according to the invention show better release properties, incrased stability of the active ingredients and excipients present, and/or improved organoleptic properties, for example appearance, odor and/or taste.

The process according to the invention can advantageously be carried out at temperatures below 200°C and preferably below 170°C, but above room temperature (25°C), preferably above 40°C. The process is carried out in particular in a temperature range which extends upward or downward by 40°C, preferably 30°C and particularly preferably 20°C, from the softening point of the mixture of components and, respectively, the melting point of the main component(s) plasticized first. It is particularly advantageous that cyclodextrin/active ingredient complexes and cyclodextrin/active ingredient complex-containing solid dosage forms can be produced with the process according to the invention at the abovementioned temperatures.

The dosage forms which can be produced by the process according to the invention may contain from 0 to 100%, preferably 0.1 to 99.5% and, in particular, 5 to 99% of the active ingredient(s) as cyclodextrin/active ingredient complex. In a preferred embodiment of the process according to the invention, at least 10%, in particular at least 30%, of the active ingredient employed is present in the form of a cyclodextrin/active ingredient complex. In another preferred embodiment of the process according to the invention, the active ingredient is essentially completely present in the form of a cyclodextrin/active ingredient complex.

The plastic mixture according to the invention is suitable, where appropriate after cooling or solidifying, for all conventional processes for producing solid dosage forms, such as granulation, grinding, compression, casting, injection molding, tableting under pressure, tableting under pressure with heat and, in particular, for extrusion and melt extrusion.

The process according to the invention can be used to shape a large number of solid dosage forms. Thus, for example, powders or granules can be produced by grinding or chopping the solidified or at least partly solidified plastic mixture, and can be either employed directly for therapy or, where appropriate with addition of conventional excipients, further processed to pellets, tablets, suppositories, implants and parenteral products.

The process according to the invention is preferably used to shape dosage forms before solidification of the plastic mixture, and these result, where appropriate after coating in any conventional way, in a form which can be employed in therapy.

The shaping to the dosage form before solidification can take place in a variety of ways, depending on the viscosity of the plastic mixture, for example by casting, injection molding, compression, nipping or calendering. This is done by conveying the plastic mixture described above to one or more shaping steps in the process according to the invention. The conveying can take place by pressing, pumping, for example with gear pumps, or, preferably, with an extruder.

It is particularly preferred for the plastic mixture to be formed in one or more, preferably one, extruder and conveyed by the latter or a downstream extruder to the shaping steps. In many cases it has proven advantageous to extrude or a downward incline and/or where appropriate provide a guide channel for transporting the extrudate, in order to ensure safe transport and prevent rupture of the extrudate. It may also be advantageous, depending on the number and compatibility of the active ingredients and/or cyclodextrin/active ingredient complexes to be employed, to employ multilayer extrudates, for example coextrudates, as described in WO 96/19963, in the process according to the invention.

The first shaping step advantageously takes place when the extrudate emerges from the extruder through suitably shaped dies, draw plates or other orifices, for example through a breaker plate, a circular die or a slit die. This usually results in a continuous extrudate, preferably with a constant cross section,

for example in the form of a ribbon or of a strand, preferably with a circular, oval, rounded or flat and broad cross section.

Suitable downstream shaping steps for extrudates are, for example, cold cut, that is to say the cutting or chopping of the extrudate after at least partial solidification, hot cut, that is to say the cutting or chopping of the extrudate while still in the plastic form, or pinching off the still plastic extrudate in a nip device. It is possible with hot or cold cut to obtain, for example, granules (hot or cold granulation) or pellets. Hot granulation usually leads to dosage forms (tablets or pellets) with a diameter of from 0.1 to 10 mm, while cold granulation normally leads to cylindrical products with a length to diameter ratio of from 1 to 10 and a diameter of from 0.5 to 10 mm. It is possible in this way to produce monolayer but also, on use of coextrusion, open or closed multilayer dosage forms, for example oblong tablets, coated tablets, pastilles and pellets. The dosage forms can be provided with a coating by convertional methods in a downstream process step. Suitable materials for film coatings are the polymers mentioned as polymeric binders, in particular polyacrylates such as the Eudragit types, cellulose esters such as hydroxypropylcellulose phthalates, and cellulose ethers such as ethylcellulose, hydroxypropylmethylcellulose or hydroxypropylcellulose and gelatin. Further shaping steps may also follow, such as, for example, rounding off the pellets obtained by hot or cold cut using rounding-off devices as described in DE-A-196 29 753.

It is particularly preferred for all the shaping steps to be carried out on the still plastic mixture or still plastic extrudate. Besides hot cut, where appropriate with subsequent rounding off, a particularly suitable process for producing the solid dosage forms is one in which the plastic mixture is shaped to the dosage form in a molding calender. This is done by conveying a still plastic mixture or a still plastic extrudate to a suitable molding calender. Suitable molding calenders usually have molding rolls and/or belts for the shaping, with at least one of the molding rolls and/or at least one of the belts having depressions to receive and shape the plastic mixture. It is preferred to use a molding calender with counterrotating molding rolls, with at least one of the molding rolls having on its surface depressions to receive and shape the plastic mixture. Suitable molding calenders and devices containing molding rolls are generally disclosed for example in EP-A-0 240 904, EP-A-0 240 906 and WO 96/19962, and suitable belts and devices

containing belts are generally disclosed for example in EP-A-0 358 105, which are incorporated herein by reference.

The shaping of the still plastic mixture or still plastic extrudate preferably takes place at temperatures below 220°C, particularly preferably below 180°C and very particularly preferably below 150°C, such as, for example, in the temperature ranges necessary to form the plastic mixture or at lower temperatures. If the shaping takes place at lower temperatures, it advantageously takes place from 5 to 70°C, preferably 10 to 50°C and particularly preferably 15 to 40°C below the highest temperature reached on formation of the plastic mixture, but preferably above the solidification temperature of the plastic mixture.

The present invention further relates to a solid dosage form which is essentially free of aliphatic C_2-C_8-di- and tricarboxylic acids and aromatic C_6-C_{10}-monocarboxylic acids and which is obtainable by a process as described above. The dosage form may comprise where appropriate organic acids such as aliphatic C_1-C_{32}-monocarboxylic acids, amino acids and amino acid derivatives. It is particularly preferred for the dosage form according to the invention to be essentially free of acids.

It is preferred for at least 10% by weight of the active ingredient to be present in the form of a cyclodextrin/active ingredient complex in the dosage forms according to the invention.

The following examples are intended to illustrate the invention without restricting it.

Examples

Extrusion took place in each case with a Werner & Pfleiderer ZKS-30 twin screw extruder with five sections under the conditions stated in the particular example.

Comparative Example 1

475 g of polyethylene glycol PEG 6000 were extruded with 25 g of β-estradiol and calendered to 1000 mg oblong tablets. Extrusion took place under the following conditions:

Section 1	20°C
Section 2	40°C
Section 3	50°C

Section 4	60°C
Section 5	50°C
Die	42°C

Release of the active ingredient from the tablets was investigated by the USP paddle method (0.1 M hydrochloric acid; pH 1.0; 150 rpm). It was 8% after 10 minutes and still below 10% after 20 and 30 minutes.

Comparative Example 2

Release of the active ingredient from the tablets of a dosage form obtained in Comparative Example 1 was determined under analogous conditions (USP; 0.1 M hydrochloric acid; pH 1.0; 150 rpm), but 150 mg of β-cyclodextrin W7M1.8 (from Wacker, methylated β-cyclodextrin with a degree of methylation of 1.8) were previously added to the test medium. The release was 8% after 10 minutes, 24% after 20 minutes and 29% after 30 minutes.

Example 1

400 g of polyethylene glycol PEG 6000 were extruded with 25 g of β-estradiol and 75 g of β-cyclodextrin W7M1.8 (from Wacker) and calendered to 1000 mg oblong tablets.

Extrusion took place under the following conditions:

Section 1	20°C
Section 2	40°C
Section 3	50°C
Section 4	60°C
Section 5	50°C
Die	42°C

Release of the active ingredient from the tablets was investigated by the USP paddle method (0.1 M hydrochloric acid; pH 1.0; 150 rpm). It was 48% after 10 minutes, 77% after 20 minutes and 80% after 30 minutes.

Comparative Example 3

400 g of polyethylene glycol PEG 6000 were extruded with 100 g of ibuprofen and calendered to 1000 mg oblong tablets.

Extrusion took place under the following conditions:

Section 1	20°C
Section 2	40°C
Section 3	50°C
Section 4	60°C
Section 5	50°C
Die	42°C

Release of the active ingredient from the tablets was investigated by the USP paddle method (0.1 M hydrochloric acid; pH 1.0; 150 rpm). It was 6% after 20 minutes, 5% after 60 minutes and 7% after 120 minutes.

Comparative Example 4

Release of the active ingredient from the tablets of a dosage form obtained in Comparative Example 3 was determined under analogous conditions (USP; 0.1 M hydrochloric acid; pH 1.0; 150 rpm), but 150 mg of β-cyclodextrin W7M1.8 were previously added to the test medium. The release was 8% after 10 minutes, 24% after 20 minutes and 29% after 30 minutes.

Release of the active ingredient from the tablets was investigated by the USP paddle method (0.1 M hydrochloric acid; pH 1.0; 150 rpm). It was 6% after 20 minutes, 9% after 60 minutes and 15% after 120 minutes.

Example 2

250 g of polyethylene glycol PEG 6000 were extruded with 100 g of ibuprofen and 150 g of β-cyclodextrin W7M1.8 and calendered to 1000 mg oblong tablets.

Extrusion took place under the following conditions:

Section 1	20°C
Section 2	40°C
Section 3	50°C
Section 4	60°C
Section 5	50°C
Die	42°C

Release of the active ingredient from the tablets was investigated by the USP paddle method (0.1 M hydrochloric acid; pH 1.0; 150 rpm). It was 18% after 20 minutes, 24% after 60 minutes and 26% after 120 minutes.

3010/ew/iT

We claim:

1. A process for producing solid dosage forms comprising as components at least one physiologically tolerated polymeric binder, at least one active ingredient and at least one cyclodextrin, wherein the components are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to the dosage form.

2. A process as claimed in claim 1, wherein the molar ratio between active ingredient and cyclodextrin is in the range from 0.1 to 4.0.

3. A process as claimed in either of the preceding claims, wherein the plastic mixture is produced by employing

   a) 0.5 to 30% by weight of at least one active ingredient,
   b) 0.5 to 70% by weight of at least one cyclodextrin,
   c) 10 to 98% by weight of at least one polymeric binder and
   d) 0 to 50% by weight of conventional excipients.

4. A process as claimed in any of the preceding claims, wherein the plastic mixture is shaped in a molding calender to dosage forms.

5. A process as claimed in claim 4, wherein a molding calender with counterrotating molding rolls is used, with at least one of the molding rolls having on its surface depressions to receive and shape the plastic mixture.

6. A process as claimed in any of the preceding claims, wherein polyaklylene glycols, alkyl celluloses, hydroxyalkyl-celluloses, polyvinylpyrrolidone, poly(hydroxy (meth)acrylates), poly(meth)acrylates, copolymers comprising monomers selected from N-vinyllactams, vinyl esters and alkyl (meth)acrylates, or mixtures thereof, are employed as polymeric binder.

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7. A process as claimed in any of the preceding claims, wherein polyethylene glycol, polyvinylpyrrolidone or copolymers comprising N-vinylpyrrolidone and vinyl acetate are employed as polymeric binder.

8. A solid dosage form which is essentially free of aliphatic C_2-C_8-di- and -tricarboxylic acids and aromatic C_6-C_{10}-monocarboxylic acids, obtainable by a process as claimed in any of claims 1 to 7.

9. A solid dosage form as claimed in claim 8, wherein at least 10% by weight of the active ingredient are present in the form of a cyclodextrin/active ingredient complex.

3010/ew/iT

A process for producing solid cyclodextrin-containing dosage forms

Abstract

The present invention relates to a process for producing solid dosage forms comprising as components at least one physiologically tolerated polymeric binder, at least one active ingredient and at least one cyclodextrin, wherein the components are mixed and plasticized at a temperature below 220°C without adding a solvent and the resulting plastic mixture is shaped to the dosage form, and to the dosage forms obtainable by this process.